Clinical trials: specific problems associated with the use of a placebo control group

T. J. M. Cleophas, J. v.d. Meulen & R. B. Kalmansohn¹

Department of Medicine, Merwede Hospital, Dordrecht, The Netherlands, and the ¹Department of Cardiology, UCLA Medical Center, Los Angeles, California, USA

The topic of placebos in clinical research has been recently addressed in general medical journals, and is relevant to a clinical pharmacologists' readership as well. In this article we try to give an overview of the benefits as well as problems of this methodology. Although the use of placebos in drug development is frequently absolutely essential, important ethical and technical problems are generally involved. We conclude that the placebo-controlled trial although methodologically pure may sometimes cause too many difficulties in the clinical setting.

Keywords: placebo, control group, clinical trials

The topic of placebos in clinical research has been recently addressed in important general journals such as the *Journal of the American Medical Association* [1], the *Lancet* [2], the *British Medical Journal* [3], and the *New England Journal of Medicine* [4]. Turner *et al.* [1] noted that the placebo response in placebo-controlled trials involves rather complex phenomena including not only psychological placebo effects but also patient expectations of being helped and characteristics of the treatment situation that influence patients to report improvement. Kleijnen *et al.* [2] assume that placebos do not adequately control for placebo effects because of unadjusted patient expectations in the course of a trial. Ernst & Resch [3] stress that the true and the perceived placebo effect may be largely different. There is, thus, growing awareness that the placebo-controlled trial is not a simple method to determine the true treatment effect of a test compound as compared to placebo. We should add that the use of placebo in patients unlike healthy subjects frequently raises ethical problems, particularly in conditions with an established treatment modality at hand [4].

In addition to pharmacokinetic and dose- or concentration-response studies, the *British Journal of Clinical Pharmacology* publishes many reprints of controlled clinical trials. Therefore this subject is relevant not only to a clinical investigator but also to a clinical pharmacologist.

Ethical problems with placebo-controlled trials

Often, for the purpose of statistical power, patients are treated for long periods of time, for example, in the many phase III mortality studies in patients with myocardial infarction: 41.4 months in SOLVD I [5], 37 months in SOLVD II [6], 42 months in SAVE [7], and 25 months in MDPIT [8]. An additional point is that quite large numbers of patients are generally involved. Lau *et al.* [9] calculated that 10 000 patients would be needed to demonstrate that a treatment reduces mortality from heart disease by 5% (with

statistical significance at $P=0.05$). Even then there is a chance of 5% that the established difference is based on an error. GISSI [10] and ISIS IV [11] included not less than 20 000 and 60 000 patients respectively. Finally, millions of dollars are required for the execution of this kind of placebo-controlled mega-trial [12], which in itself is in striking contrast with the current context of relative scarcity that even in the Western world is starting to characterize health care.

The ethicist Immanuel Kant [13] emphasizes the primacy of the test subject: human beings by virtue of their unique capacity of rational thought have an inherent dignity which makes them superior to animals. It implies that they should not be used as means to an end but rather as ends in themselves. The essence of this statement can be recognized in the first lines of the Declaration of Helsinki [14], which investigators worldwide are compliant with: 'A physician shall act only in the patient's interest'. It indicates that we should not subjugate the welfare of an individual to the needs of society. Yet, basically, that is what clinical trials do. This principle seems to be inconsistent, in particular, with the prescription of a placebo to a patient. This principle is one of the reasons that oncologists decide that in their speciality placebo-controlled trials are only acceptable for support care indications and not for the treatment of the disease. How do specialists other than oncologists justify the use of such trials for the latter purpose. On the one hand, it seems ethical to prove that the efficacy of a new treatment is not entirely based on a placebo effect. On the other hand, it may not be very ethical to do so by treating a group of diseased persons with a placebo throughout a trial. A placebo is definitely inappropriate in life-threatening conditions with a well-established effective, albeit imperfect, treatment modality available. In this situation the new treatment should be tested either against the standard treatment or in addition to the standard treatment. If this is not available, is it ethical to use a placebo then? Perhaps not always, for example, if we have strong arguments to believe that the new treatment is indeed better than placebo which in many phase III trials is definitely so. We should add that in clinical

medicine it is far from uncommon to base decisions on beliefs rather than proven facts.

Benefits of placebo-controlled trials

The most important reasons for the initiation of placebo-controlled trials are the following. First, this type of trial which is purely experimental in nature provides the rigor which is required for the generation of the most reliable data. The clinical trial even though it has problems, is in fact an essential methodology in drug development. In many situations, use of a placebo is absolutely essential. The most classic examples of this are the Cast Trials [15–17]. For many years physicians had treated patients with antiarrhythmic drugs in an effort to reduce mortality and were actually increasing mortality. Secondly, investigators often use the argument that the interest of the community at large is superior to the interest of a group of individuals, when arguing placebo-controlled testing of potentially important compounds. For example, Yusuf *et al.* [18], and Antman *et al.* [19] use this argument to justify the appropriateness of a placebo group in large, simple randomized trials such as ISIS [11] or VHeFT [20], particularly in the setting where the effectiveness of a putative treatment is unknown or, at least, unproven. We should add that the ability of a clinical trial subject to give consent to participate in those placebo-controlled studies has been extensively debated and confirmed by medical ethicists [21–24]. Thirdly, in countries such as the USA and the UK new pharmaceutical compounds may not be registered until randomized placebo-controlled trials have provided sufficiently powerful data, even though poor recruitment is hampering this type of research [25]. The problem is that in the absence of a placebo group, clinical trials would contain only an active control. A trial comparing only two or more active treatments, in general, needs to be appreciably larger than a placebo-controlled study, since showing comparability between active treatments in the absence of a placebo is without meaning if a study is insufficiently powered to be able to detect a meaningful difference. If a new, 'active' treatment is actually ineffective, then a placebo-controlled trial may minimize the number of individuals ultimately exposed to the ineffective treatment, arguably an ethically desirable outcome.

Technical problems with placebo-controlled trials

The evidence provided by placebo-controlled studies is, however, often considerably smaller than one might think. Consider a significant difference from placebo at $P=0.03$, such as, for example, demonstrated in a subanalysis of the SOLVD study [26]. This means that a chance of 3% exists that the conclusion should have been 'no difference' and a power of only 70% exists that the conclusion 'true difference' is justified. An additional point is the issue of little clinical relevance in spite of statistically significant findings. The above mentioned subanalysis for instance found no symptoms of angina pectoris in 85.3% of the patients on enalapril and in 82.5% of the patients on placebo [27]. In such a situation one has to wonder about the clinical relevance of this small difference. This is particularly so when considering that an active compound generally causes more side-effects than a

placebo. Finally, we have to consider the point of bias. Arguments have been raised that placebo-controlled trials and particularly the placebo-arm of such trials are especially vulnerable to bias [28]. Although intended to control for psychologic effects, they create an atmosphere of increased risks of such effects at the same time. For example, in clinical trials, as opposed to regular patient care, patients are generally highly compliant; their high compliance is an important reason for participating in the trial in the first place. They have a positive attitude towards the trial and anticipate personal benefit from it, a mechanism which in the psychology literature is known as the Hawthorne effect [29]. Also, they do not want to disappoint the investigators who are showing so much interest in them. These mechanisms may enhance the placebo response on the part of the participants. On the part of the investigators it may be extremely difficult to reveal the complete truth about the placebo, and the potential of a trial is usually 'talked up'. Furthermore, many phase III trials fail to obtain a written informed consent about the placebo [30, 31]. Therefore, the clinical trial, although intended to control for placebo effects, simultaneously creates an atmosphere of increased risks of such effects. An enhanced placebo effect can also occur as a consequence of carryover effect from the active treatment into the placebo treatment in crossover studies, and as a consequence of asymmetric placebo groups in parallel-group studies. Even if bias affects both of the treatment modalities similarly, it is likely to damage the placebo data to a greater extent. This is because placebo data are usually small, and small effects are more vulnerable to a fixed amount of bias than large effects [32]. An additional problem of placebo-controlled studies is the fact that selected patients often refuse to comply with randomization. The remaining sample may be small and unrepresentative, and its relevance to the patients' population at large becomes difficult to judge. If at the end of these laborious efforts, including the recruitment of patients from different facilities, the results do not confirm the expectations of the investigators, one has to wonder if we should use alternative methods for the evaluation of new treatment modalities more often.

Conclusions

In recent decades secondary prevention trials and mortality studies, particularly in patients with myocardial infarction, have frequently made use of placebo controls. Some of us would say that, with life-threatening diseases, obtaining the greatest reliability about the effect of the treatment on death is more important than the ethical problems that may be involved in such an approach. Others, however, will not automatically agree on this point and will find that mortality as endpoint had better be replaced by morbidity more often, because the latter provides not only better sensitivity but also less ethical problems. Such endpoint may then be used as a surrogate endpoint to estimate mortality. We should add that it is not necessarily the case that morbidity parallels mortality—witness the case with the phosphodiesterase inhibitor vasodilators in the treatment of congestive heart failure and hypertension where a variety of drugs improved exercise tolerance and even provided symptom benefit to patients at

the expense of a significant increase in mortality [33, 34]. Although placebo-controlled experimental research generally provides greater reliability than other forms of research, this very method sometimes causes major problems within the structure of a clinic where individual treatments of patients is the priority. As a consequence of bias results may lose their scientific value. Case-control studies, retrospective and prospective cohort studies, and observational studies, although currently little used in the evaluation of a new drug or therapy, may be acceptable alternatives, that could be the methods of choice, if the gold standard although methodologically pure, causes too many difficulties in the clinical setting.

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